the actin cytoskeleton in podocytes.[13] The same may be true for high-dose DEXA.[14]

Currently, the treatment of FSGS can be considered as a voyage between Scylla and Charybdis. On one hand, we need to use prolonged aggressive therapy in patients with idiopathic FSGS who may respond, although response may take at least 4 months of therapy. On the other hand, many patients with FSGS do not have idiopathic FSGS and will not respond to conventional immunosuppressive therapy, and such exposure will put these patients at risk. The debate on the best treatment options for FSGS will continue. Since FSGS is not one disease, it is not surprising that the literature data on FSGS are so heterogeneous, results being dependent on the composition of the study population. The FSGS trial clearly illustrates that randomized controlled trials are difficult to perform. Before embarking on new intervention studies, we need to develop better clinical definitions for patients with FSGS, based on strict diagnostic and prognostic criteria. Prospective registry data could provide these criteria. In addition, studies must be directed at identifying risk markers for progression and outcome.

DISCLOSURE
The authors declared no competing interests.

SUPPLEMENTARY MATERIAL
Table S1. Remission rate in studies in patients with steroid resistant FSGS using prolonged and/or high dose corticosteroid therapy.
Table S2. Remission rate in studies in patients with steroid resistant FSGS using calcineurin inhibitors with/without high dose corticosteroids.
Supplementary material is linked to the online version of the paper at http://www.nature.com/ki

REFERENCES
1. Deegens JK, Steenbergen EJ, Wetzels JF. Review on diagnosis and treatment of focal segmental glomerulosclerosis. *Neth J Med* 2008; **66**: 3–12.
2. Troyanov S, Wall CA, Miller JA *et al.* Focal and segmental glomerulosclerosis: definition and relevance of a partial remission. *J Am Soc Nephrol* 2005; **16**: 1061–1068.
3. Gipson DS, Trachtman H, Kaskel FJ *et al.* Clinical trial of focal segmental glomerulosclerosis in children and young adults. *Kidney Int* 2011; **80**: 868–878.
4. Gipson DS, Trachtman H, Kaskel FJ *et al.* Clinical trials treating focal segmental glomerulosclerosis should measure patient quality of life. *Kidney Int* 2011; **79**: 678–685.
5. Gipson DS, Chin H, Presler TP *et al.* Differential risk of remission and ESRD in childhood FSGS. *Pediatr Nephrol* 2006; **21**: 344–349.
6. Cattran D, Appel G, Hebert L *et al.* A randomized trial of cyclosporine in patients with steroid-resistant focal segmental glomerulosclerosis. North America Nephrotic Syndrome Study Group. *Kidney Int* 1999; **56**: 2220–2226.
7. Ponticelli C, Rizzoni G, Edefonti A *et al.* A randomized trial of cyclosporine in steroid-resistant idiopathic nephrotic syndrome. *Kidney Int* 1993; **43**: 1377–1384.
8. Cattran DC, Wang MM, Appel G *et al.* Mycophenolate mofetil in the treatment of focal segmental glomerulosclerosis. *Clin Nephrol* 2004; **62**: 405–411.
9. Li Z, Duan C, He J *et al.* Mycophenolate mofetil therapy for children with steroid-resistant nephrotic syndrome. *Pediatr Nephrol* 2010; **25**: 883–888.
10. Segarra A, Vila J, Pou L *et al.* Combined therapy of tacrolimus and corticosteroids in cyclosporin-resistant or -dependent idiopathic focal glomerulosclerosis: a preliminary uncontrolled study with prospective follow-up. *Nephrol Dial Transplant* 2002; **17**: 655–662.
11. Meyrier A, Noel L, Auriche P *et al.* Long-term renal tolerance of cyclosporin A treatment in adult idiopathic nephrotic syndrome. Collaborative Group of the Societe de Nephrologie. *Kidney Int* 1994; **45**: 1446–1456.
12. Genovese G, Friedman DJ, Ross MD *et al.* Association of trypanolytic ApoL1 variants with kidney disease in African Americans. *Science* 2010; **329**: 841–845.
13. Faul C, Donnelly M, Merscher-Gomez S *et al.* The actin cytoskeleton of kidney podocytes is a direct target of the antiproteinuric effect of cyclosporine A. *Nat Med* 2008; **14**: 931–938.
14. Ransom RF, Lam NG, Hallett MA *et al.* Glucocorticoids protect and enhance recovery of cultured murine podocytes via actin filament stabilization. *Kidney Int* 2005; **68**: 2473–2483.

see original article on page 879

Transplant glomerulopathy: it's not always about chronic rejection

Mark Haas[1]

Transplant glomerulopathy (TG) is a morphologic lesion of renal allografts characterized by duplication of the glomerular basement membrane and is widely accepted as a manifestation of chronic antibody-mediated rejection (AMR). However, TG is not specific for chronic AMR, and this pattern of injury may result from a number of disease processes affecting the glomerular endothelium. Baid-Agrawal and co-workers consider three different, but not mutually exclusive, processes that can produce morphologic lesions of TG: chronic AMR, hepatitis C, and thrombotic microangiopathy.

Kidney International (2011) **80,** 801–803. doi:10.1038/ki.2011.192

Transplant glomerulopathy (TG) is a morphologic lesion of renal allografts that is characterized histologically by duplication and/or multilayering of the glomerular basement membrane. It is best appreciated on tissue sections stained with silver stains that highlight the glomerular basement membrane (Figure 1) and is only infrequently seen before 1 year post-transplantation,[1,2] although earlier lesions may be appreciated by electron microscopy.[3] TG, and the closely related lesion of peritubular capillary (PTC) basement membrane multilayering, are felt to represent manifestations of chronic rejection, particularly chronic antibody-mediated rejection (AMR).[4] TG is well documented to be associated with the presence of antibodies against the renal allograft, most notably antibodies against human leukocyte antigen class II antigens, and the presence of histologic lesions of TG on a renal allograft biopsy is a predictor of reduced long-term graft survival.[2,5]

Sis and co-workers[6] included TG, together with PTC basement membrane multilayering, PTC C4d deposition, and donor-specific antibodies (DSAs), in their 'ABCD tetrad' indicative of chronic-active AMR in renal allografts. However, only 73% of their cases of TG were associated

[1]*Department of Pathology and Laboratory Medicine, Cedars-Sinai Medical Center, Los Angeles, California, USA*
Correspondence: *Mark Haas, Department of Pathology and Laboratory Medicine, Cedars-Sinai Medical Center, 8700 Beverly Boulevard, Los Angeles, California 90048, USA. E-mail: mark.haas@cshs.org*

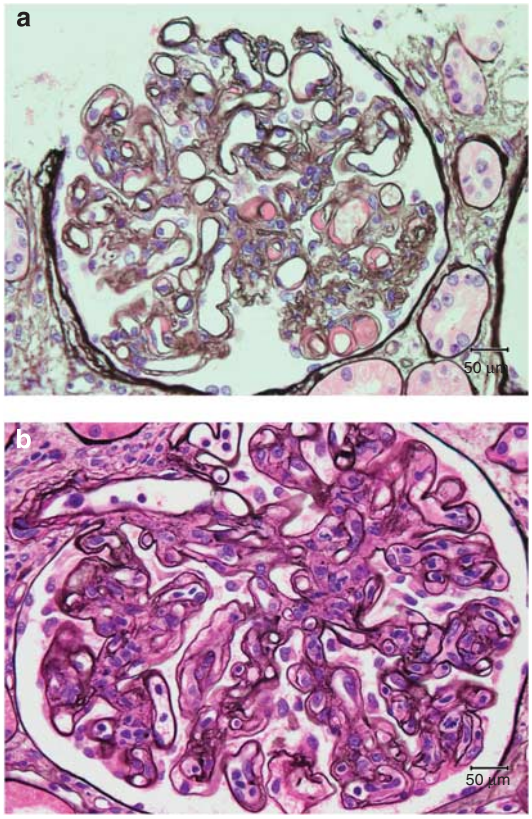

Figure 1 | Histologic lesions of transplant glomerulopathy in renal allograft biopsies. (**a**) Multiple double contours of the glomerular basement membrane (GBM) are apparent on the silver methenamine stain. Segmental glomerulosclerosis is also present, with associated protein insudates that appear pink on this stain. There is minimal glomerulitis present, and this lesion of transplant glomerulopathy (TG) is easily differentiated from membranoproliferative glomerulonephritis (MPGN). (**b**) In addition to TG with GBM double contours, this glomerulus also shows severe, active glomerulitis with numerous intracapillary leukocytes and mild lobular accentuation. As such, this lesion cannot be definitely distinguished from MPGN, although the latter was ruled out by the absence of immune complex deposits by immunofluorescence and electron microscopy. (**a** and **b**, silver methenamine stain; original magnification, ×400).

with DSA or C4d, leaving more than one-fourth of cases of TG outside of this tetrad. Several studies (for example, Cosio *et al.*[2,7]) had suggested an association between hepatitis C virus (HCV) and TG in renal allografts; however, in these studies most or all biopsies were examined by light microscopy only. HCV is associated with, and is felt to be a causative agent of, recurrent and *de novo* membranoproliferative glomerulonephritis (MPGN) in renal allografts,[8] and by light microscopy alone TG can closely resemble MPGN, particularly if the former is accompanied by active transplant glomerulitis (Figure 1). Another potential cause of TG unrelated to alloantibody could be thrombotic microangiopathy (TMA), which has multiple potential etiologies, including calcineurin inhibitor (CNI) nephrotoxicity.[9] TMA is manifest by injury to endothelial cells and, in a chronic or smoldering form, can produce a pattern of glomerular injury with prominent GBM duplication.

Baid-Agrawal and co-workers[10] (this issue) examine these three potential causes of TG in a series of 25 renal allograft biopsies, performed for evaluation of chronic renal allograft dysfunction and/or proteinuria. In all 25 biopsies, MPGN was ruled out, as no immune complex deposits were seen by immunofluorescence and/or electron microscopy. In at least 21 of these, possibly as many as 24 (including three cases with chronic CNI toxicity without diagnostic changes of TMA), the changes of TG could be accounted for by alloantibody (C4d deposition in PTC, with *de novo* DSA in seven of eight cases with available serum), HCV, and/or TMA. Fifteen biopsies with diagnostic changes had only one cause of TG (nine alloantibody, three HCV, three TMA), while six others had HCV and C4d or HCV and TMA. TMA and HCV were often seen together; the majority of biopsies from HCV-positive patients had findings of TMA, and vice versa.[10] A particularly notable finding was that graft survival from the time of transplantation, as determined by time-to-event (Kaplan–Meier) analysis, was significantly shorter in HCV-positive patients with TG than in HCV-negative patients with TG.[10]

A potential shortcoming of this study[10] is the use of C4d staining to define cases of TG caused by alloantibody, with DSA data at the time of biopsy available in only 12 of 25 cases. Sis and co-workers[11] have defined a subgroup of renal allograft biopsies showing antibody-induced graft injury in the absence of C4d, defined by expression of endothelial transcripts and the presence of DSA. Furthermore, Loupy *et al.*[12] found that TG may develop in the presence of DSA in grafts showing glomerulitis and/or peritubular capillaritis, without C4d. Still, in the study of Baid-Agrawal *et al.*,[10] two HCV-positive patients with TG and negative C4d also had negative DSA, suggesting that in at least some cases HCV can produce TG in the absence of alloantibody.

How might HCV infection produce morphologic lesions of TG in these latter cases? One possibility might involve low levels of immune complex deposits and/or cryoglobulins producing MPGN-type lesions, with resorption of these glomerular deposits prior to biopsy. Alternatively, and perhaps more likely, noting the frequent overlap of HCV and TMA in the lesions of TG studied by Baid-Agrawal *et al.*,[10] HCV may produce a lesion of TMA involving the glomeruli. In an earlier study of 18 renal allograft recipients who were HCV-positive at the time of transplantation, Baid *et al.*[13] found that five patients developed TMA between 5 and 120 days post-transplantation, and that all five had anti-cardiolipin antibodies. By contrast, only one of 13 HCV-positive patients without TMA and none of seven HCV-negative patients with recurrent or *de novo* TMA had anti-cardiolipin antibodies.[13]

As is noted above, the presence of TG on a renal allograft biopsy is associated with poor graft survival,[2,5] and the data of Baid-Agrawal *et al.*[10] indicate that graft survival with TG is even worse in HCV-positive patients. However, regardless of the etiology, there is no significant evidence at

present that histologic lesions of TG are reversible with therapy, whether this be removal of DSA, treatment of HCV, lowering of CNI dose, or other treatment, and once TG is apparent by light microscopy, the fate of the graft may already be sealed.

Indeed, an important key to prolonging graft survival would appear to be prevention of TG, and in this regard, recognizing those grafts at high risk for developing TG is an important step toward this goal. Our findings in patients with DSA, glomerulitis, and/or peritubular capillaritis, and early ultrastructural findings that have been reported in grafts that later develop TG,[3] suggest that early treatment with intravenous immunoglobulin, plasmapheresis, and/or rituximab may prevent or at least delay the onset of TG.[14] By expanding the list of potential etiologies of TG, Baid-Agrawal and co-workers[10] have opened the door for studies of early treatment of other potential causes of TG, particularly HCV. It will also be important to determine whether there are specific subsets of HCV-positive allograft recipients who are at greatest risk for developing TG, just as DSAs against human leukocyte antigen class II antigens are most closely associated with TG.[2,5] For example, does HCV-associated TG occur significantly more often, or earlier post-transplantation, when there is also evidence of TMA? If so, might the presence of anti-cardiolipin antibodies represent an important risk factor for development of TG in these patients? Are HCV-positive graft recipients treated with CNI-sparing immunosuppressive regimens less likely to develop TG than patients receiving standard doses of CNIs?

In summary, it is important for us to recognize that TG is not a specific diagnosis that can be equated with chronic or chronic-active AMR but is rather a pattern of graft injury with a number of non-mutually-exclusive etiologies that now include HCV and TMA in addition to AMR. More importantly, we can now focus even more on determining which patients among those with alloantibody, HCV, and/or TMA are at greatest risk for developing TG and why, and what can be done therapeutically to reduce this risk.

DISCLOSURE
The author declared no competing interests.

REFERENCES
1. Habib R, Zurowska A, Hinglais N *et al.* A specific glomerular lesion of the graft: allograft glomerulopathy. *Kidney Int* 1993; **44**(Suppl 42): S104–S111.
2. Cosio FG, Gloor JM, Sethi S, Stegall MD. Transplant glomerulopathy. *Am J Transplant* 2008; **8**: 492–496.
3. Wavamunno MD, O'Connell PJ, Vitalone M *et al.* Transplant glomerulopathy: ultrastructural abnormalities occur early in longitudinal analysis of protocol biopsies. *Am J Transplant* 2007; **7**: 1–12.
4. Regele H, Bohmig GA, Habicht A *et al.* Capillary deposition of complement split product C4d in renal allografts is associated with basement membrane injury in peritubular and glomerular capillaries: a contribution of humoral immunity to chronic allograft rejection. *J Am Soc Nephrol* 2002; **13**: 2371–2380.
5. Gloor JM, Sethi S, Stegall MD *et al.* Transplant glomerulopathy: subclinical incidence and association with alloantibody. *Am J Transplant* 2007; **7**: 2124–2132.
6. Sis B, Campbell PM, Muller T *et al.* Transplant glomerulopathy, late antibody-mediated rejection and the ABCD tetrad in kidney allograft biopsies for cause. *Am J Transplant* 2007; **7**: 1743–1752.
7. Cosio FG, Roche Z, Agarwal A *et al.* Prevalence of hepatitis C in patients with idiopathic glomerulopathies in native and transplant kidneys. *Am J Kidney Dis* 1996; **28**: 752–758.
8. Cruzado JM, Carrera M, Torras J, Grinyo JM. Hepatitis C virus infections and *de novo* glomerular lesions in renal allografts. *Am J Transplant* 2008; **1**: 171–178.
9. Naesens M, Kuypers DRJ, Sarwal M. Calcineurin inhibitor nephrotoxicity. *Clin J Am Soc Nephrol* 2009; **4**: 481–508.
10. Baid-Agrawal S, Farris III AB, Pascual M *et al.* Overlapping pathways to transplant glomerulopathy: chronic humoral rejection, hepatitis C infection, and thrombotic microangiopathy. *Kidney Int* 2011; **80**: 879–885.
11. Sis B, Jhangri G, Bunnag S *et al.* Endothelial gene expression in kidney transplants with alloantibody indicates antibody-mediated damage despite lack of C4d staining. *Am J Transplant* 2009; **9**: 2312–2323.
12. Loupy A, Suberbielle-Boissel C, Hill GS *et al.* Outcome of subclinical antibody-mediated rejection in kidney transplant recipients with preformed donor-specific antibodies. *Am J Transplant* 2009; **9**: 2561–2570.
13. Baid S, Pascual M, Williams Jr WW *et al.* Renal thrombotic microangiopathy associated with anticardiolipin antibodies in hepatitis C-positive renal allograft recipients. *J Am Soc Nephrol* 1999; **10**: 146–153.
14. Haas M, Mirocha J. Early ultra structural changes in renal allografts: correlation with antibody - mediated rejection and transplant glomerulopathy. *Am J Transplant* 2011; in press (doi: 10.1111/j.1600-6143.2011.03647.x)

see original article on page 886

Olfactory function in dialysis patients: a potential key to understanding the uremic state

Andrew S. Bomback[1] and Amanda C. Raff[2]

Impaired olfactory function is a marker of neurologic dysfunction in the uremic state. Retained uremic toxins not adequately cleared with dialysis may undermine the integrity of the olfactory epithelium and olfactory bulb and malign central olfactory processing. The evidence suggests that only renal transplantation, with its concomitant thorough reversal of uremia, truly restores olfactory function to normal in end-stage renal disease. Testing of olfactory function may emerge as an important marker for the extent and resolution of uremia.

Kidney International (2011) **80,** 803–805. doi:10.1038/ki.2011.219

[1]*Division of Nephrology, Department of Medicine, Columbia University College of Physicians and Surgeons, New York, New York, USA and* [2]*Department of Medicine, Albert Einstein College of Medicine and Montefiore Medical Center, Bronx, New York, USA*
Correspondence: *Andrew S. Bomback, Columbia University Medical Center, 622 West 168th Street, Ph 4-124, New York, New York 10032, USA. E-mail: asb68@columbia.edu*

The excessive morbidity and mortality that afflicts the end-stage renal disease (ESRD) population on maintenance dialysis has received significant attention in both the medical and the mass-market literature. While these depressing statistics should by no means be ignored, what often strikes dialysis providers rounding in outpatient units is the poor day-to-day